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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,631	04/11/2005	Seiichi Araki	T0509.70011US00	5167

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EXAMINER	
HUGHES, ALICIA R	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
03/03/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,631	ARAKI ET AL.	
	Examiner	Art Unit	
	ALICIA R. HUGHES	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims and Examination

Claims 15 and 19 are pending and the subject of this Office Action.

Applicants' arguments filed on 17 September 2009 have been fully considered, but are not deemed to be persuasive regarding the previous rejection. Rejections not reiterated from this Office's previous action are hereby withdrawn. The rejections set forth herein constitute the complete set of rejections being applied to the instant application presently.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grimble, et al as evidenced by Grimble II.

The teachings of Grimble et al I and Grimble et al II previously made of record are incorporated herein by reference in total. This Office's previous teachings of Grimble, et al I and Grimble et al II in the Office Action of 27 August 2007, 11 July 2008, and 18 March 2009 are incorporated herein by reference, in total.

Applicant continues to argue that the Grimble references merely teach glutathione as a major endogenous antioxidant and that riboflavin and vitamin B6 merely participate in glutathione status, but there is no direct correlation between glutathione or its production

pathway, riboflavin and cytokine production and no teaching in the Grimble references that riboflavin prevents increased cytokine production.

Additionally, Applicant argues that the cited references do not render the instant claims obvious, but rather, merely teach that riboflavin, among other vitamins, is an important nutrient that is necessary in maintaining a general balance of the body's immune system. Moreover, Grimble et al I and Grimble et al II do not teach or suggest that riboflavin per se would be effective in preventing hypercytokinemia. Applicant argues that to the contrary, the cited references describe many possible nutrients that may have the property that applicants discovered in riboflavin phosphate, and that this possibility is not proof capable of supporting an obviousness rejection, as it is only and example of an obvious to try rationale. Applicants further argue that the Examiner has reached her conclusion based on hindsight construction.

As noted prior, Applicant continues to argue that the cited references do not teach or suggest any relationship between riboflavin and cytokines. However, just as noted prior, the Examiner finds Applicants' responses wholly unpersuasive because the disclosures in Grimble, RF, "Effect of Antioxidative Vitamins on Immune Function with Clinical Applications. International J. Vitam. Nutr. Res., Vol. 67, No. 5, pages 312-320 (1997)[hereinafter referred to as "Grimble, et al I"],[1] coupled with the state of the art at the time that the invention was disclosed, supports otherwise. *Please see generally*, Grimble, Robert, "Modification of Inflammatory Aspects of Immune Function by Nutrients," Nutrition Research, Vol. 18, No. 7, pages 1297-1317 (1998)[hereinafter referred to as "Gimble II"]. Examiner respectfully disagrees with all of the aforementioned arguments by Applicant.

[1] Previously cited on PTO-892 of 24 March 2006.

In support of Applicant's arguments, the Applicant says that the extent of immune responses is "influenced by a number of factors" and citing a line from Grimble et al I, that "[t]he interaction between the response of the immune system to pathogens and inflammatory agents, and antioxidative vitamins is complex" (Grimble et al I, Page 317, Col. 2). However, rather than continue the important rationale behind that statement in Grimble et al I, Applicant stops. It is important, however, to note that as a follow-up to the statement of complexity, Grimble et al I immediately thereafter states, "However, two common themes emerge amidst the complexity (Figure 4). The first of these is the influence of antioxidant defense upon the immune response"(Grimble et al I, Page 317, Col. 2). Grimble et al I goes on further to teach, "The second of the themes may relate to intracellular glutathione concentrations" (Grimble et al I, Page 318, Col. 1). It is these teachings, primarily, that negate Applicant's arguments. The suggestion to try Applicant's invention arises from these teachings coupled with the below, as noted prior.

At the time the present invention was disclosed, it was well-known in the art that there is a direct correlation between the functionality of balanced cytokine production when reacting to an inflammatory response and the activity of the glutathione production pathway to limit the creation of excessive cytokines (See Grimble II, page 1308, latter portion of Conclusion paragraph 3).[2] It has been known for quite some time that "[c]ytokines play a crucial role as modulatory agents by which the activity of the system is changed and metabolic activity of the host directed towards provision of nutrients for the system from endogenous sources. Nutrient

[2] The high priority given to combating pathogens is necessary because of the speed with which pathogens multiply once established within the host. In general terms, bacterial cells multiply at least 50 times as rapidly as T cells under favorable conditions. Thus, the provision of nutrients to allow the immune system to function correctly cannot be left to chance.

intake, prior to infection will influence the extent of endogenous nutrient provision." *(Grimble II, Page 1308)* Glutathione is defined as a "major endogenous antioxidant," and "[v]itamin B_6 and riboflavin participate in the maintenance of glutathione status" (See Abstract). Thus, endogenous nutrient provision, i.e. glutathione production, controls hyperactivity of cytokines, or hypercytokinemia, and "[v]itamin B6 and riboflavin participate in the maintenance of glutathione status" (See Abstract).

As noted prior, "[d]eficiencies in vitamins E, B_6 and riboflavin reduce cell numbers in lymphoid tissues of experimental animals and produce functional abnormalities in the cell mediated immune response." *(Abstract)*. Thus, where there is a deficiency in riboflavin, endogenous nutrient provision provided by glutathione will lack, thereby creating a heightened immune/inflammatory response that wields the over- or hyper-production of cytokines. Therefore, if a deficiency in riboflavin contributes to a heightened inflammatory response then it logically flows mechanistically that the presence of riboflavin has an inverse relationship with cytokine production as an immune response. It is the establishment of this relationship that makes the prior art rejection in Grimble, et al applicable to the instant invention.

Finally, Applicant has provided a declaration from Dr. Kohtaro Kodama. Examiner has closely examined the declaration, but on deciding the issue of whether the data therein indicates that vitamin B2 has no effect on glutathione levels in erythrocytes in LPS-treated rats and mice, the data is not conclusive and therefore, is unpersuasive. Specifically, LPS + Vitamin B2 showed a rise in glutathione concentration in rats (19.4 to 20.3) whereas LPS + Vitamin B2 showed a decrease in mice (17.4 to 15.8). One result essentially neutralizes the other, making the data inconclusive.

In view of the foregoing, the rejection is sustained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alicia Hughes whose telephone number is 571-272-6026. The examiner can normally be reached from 9:00 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR of Public PAIR. Status information for unpublished applications is available through Public PAIR only. For information about the PAIR system, see http://pair-direct-uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alicia R. Hughes/

Examiner, Art Unit 1614

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614